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Original article

Characteristics of COVID-19 patients admitted into two hospitals in sapporo, Japan: Analyses and insights from two outbreak waves

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ABSTRACT

Background: Coronavirus disease (COVID-19) emerged in January 2020 in Sapporo city, and the outbreak has shown two peaks.
Methods: A total of 260 COVID-19 patients were enrolled and categorized into three groups according to the pandemic pattern, jobs and situation, and disease severity. We compared clinical characteristics according to these categories.
Results: We found two pandemic peaks, and the proportion of patients and health providers who were infected in other hospitals had increased in the latter two periods (period 2: 49.6%, period 3: 32.7%). Particularly, the proportion of infected health providers was 27% in period 2, and they tended to be younger females with a mild condition. Severity of the disease (requirement of oxygen and/or mechanical ventilation) was associated with advanced age, and all the patients who died during admission were over 60 years old.
Conclusions: We reported the temporal dynamics and characteristics of the COVID-19 pandemic in Sapporo city, Japan. This survey from the viewpoint of the hospital provides a new insight into and a better guide for the further management of the COVID-19 pandemic.
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1. Introduction

A novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China toward the end of 2019 and has caused an unprecedented outbreak of pneumonia, named coronavirus disease (COVID-19), in China and many parts of the world [1,2]. A COVID-19 outbreak started in Sapporo city ahead of other areas in Japan, likely due to a large event that took place at the beginning of February. The Hokkaido Governor had declared a state of emergency twice, independent of the Japan central government. Due to these declarations, the number of infected cases in Sapporo city has decreased, and the outbreak has been shown to have two clear peaks to date.

Epidemiological information on the COVID-19 outbreak has been disseminated by the government and each prefecture in Japan, which is helpful for our understanding of the drastic changes during the outbreak and for managing the social and medical strategies for preventing further spread of the pandemic. However, this information is limited; as a result, we believe that the survey from the viewpoint of hospitals will provide new insights into and a better guidance for managing changes during the COVID-19 pandemic. At the time of writing this manuscript (middle of August 2020), Sapporo city had experienced two clear spikes in the number of cases during the outbreak. However, the clinical differences in the characteristics of patients during these two spikes have not been determined. In addition, we could not obtain the clinical differences based on the disease severity and patients' job/situation. In this study, we retrospectively analyzed the clinical characteristics of patients who were diagnosed with COVID-19 in two hospitals in Sapporo before August 21, 2020. We specifically aimed to determine the clinical differences among patients according to the study period, severity, and patients' jobs/situation, which could be obtained by the survey from the government viewpoint.

2. Materials and methods

2.1. *Study subjects*

The Sapporo city administration has made adjustments to medical facilities that would admit COVID-19 patients based on the degree of severity and the state of the infection. During the early phase, all patients who had a positive PCR test for SARS-CoV-2 required hospitalization in quarantine. During the later phase, accommodations for those with no or mild symptoms were provided. Based on repeated discussions with the directors of many hospitals and the Sapporo city administration, the Hokkaido Medical Center and Sapporo Medical University Hospital were designated to accept patients with a wide range of severity, ranging from mild to severe, who required hospitalization. Therefore, we analyzed the characteristics of the patients admitted in these two hospitals: Hokkaido Medical Center ($n = 154$) and Sapporo Medical University Hospital ($n = 106$), between February 26 and August 21, 2020. The diagnosis of COVID-19 in each patient was based on a positive nasopharyngeal PCR result [1,2]. The protocol for this study was approved by the ethics committee of each hospital. The severity of the COVID-19 infection was defined by the guidelines on the clinical management of patients with COVID-19, with mild cases consisting of those not requiring oxygen administration, moderate cases as those requiring oxygen, and severe cases as those requiring mechanical ventilation. Basically, the treatment strategy followed the official Japanese guidelines that were developed by the Ministry of Health, Labour, and Welfare [3].

2.2. *Social events in sapporo during the observational period*

The first case of COVID-19 infection in Japan was confirmed on January 28, 2020 in Hokkaido, three days after the Spring Festival in China (formerly "Chinese New Year"). The infected individual was a Chinese woman in her 40s who had visited Hokkaido from Wuhan city, China, on January 21, 2020. Thereafter, approximately two million tourists from various countries including China visited Sapporo for the Sapporo Snow Festival, which was held from January 31 to February 11. After the second infected individual was confirmed on February 14, 2020, the number of infected individuals started to increase, and on February 28, the governor of Hokkaido declared a state of emergency.

The first state of emergency declaration was made over the period from February 28 to March 19, and individuals had to observe the following rules: (1) thorough measures to prevent the spread of infection, (2) requests to stay at home, (3) requests to stop using facilities and holding events (cooperation requested), and (4) promotion of social distancing. Subsequently, the number of infected patients decreased. However, as the number of infected individuals started to increase again, a second declaration of a state of emergency was made over the period from April 17 to May 24.

According to the data provided by Agoop, Co., Ltd. (https://www.agoop.co.jp/contact-analysis-coronavirus/), the population of central Sapporo city (Sapporo station, Ohdori park, and Susukino) decreased by approximately 21% based on the average data three weeks before and after the first declaration of a state of emergency, and by approximately 57% after the second declaration.

2.3. *Statistical analyses*

Continuous data are presented as means and medians, whereas categorical data are presented as frequencies and proportions. To compare differences among the groups, Mann-Whitney *U* test was used for nonparametric continuous variables, and the chi-square test was used for categorical variables. Statistical analyses were performed using the statistical software package JMP version 13 (SAS Institute Inc., Cary, NC) and SAS version 9.3 (SAS institute, Cary, NC, USA). For all statistical analyses, $P < 0.05$ was considered significant.

3. Results

3.1. *Characteristics of patients enrolled in this study*

Table 1 shows the characteristics of the 260 patients. The median age was 62 years, and 129 patients (49.6%) were males. Regarding disease severity, 55 patients (21.2%) were moderate, 35 (13.5%) were severe, and 8 patients (3.1%) underwent extracorporeal membrane oxygenation (ECMO). Of 260 patients, 15 (5.9%) died due to respiratory failure. Among the patients who were discharged alive, 112 (43.1%) went back to their homes, 65 (25.0%) went to accommodation facilities, 60 (23.1%) were sent to another hospital, and 8 (3.1%) were still in either of the two hospitals. Based on the chest CT images, 221 of 260 (85%) patients had abnormal findings suggesting a pneumonia.

3.2. *Comparison of the clinical characteristics of patients according to the three categorized periods*

Fig. 1A shows the number of patients newly diagnosed with COVID-19 during the study period in Sapporo city. (Data provided by Sapporo city; https://www.city.sapporo.jp/hokenjo/f1kansen/2019n-covhassei.html). A total of 948 patients were diagnosed during our observation period (February 26 to August 9). The number of patients diagnosed in the two hospitals (Fig. 1B) was similar to that of the whole Sapporo city. Based on these two figures, visually and for convenience, we considered that the first wave lasted until March 31 (period 1), the second wave was from April 1 to May 20 (period 2), and the latter dates fell under the third period (period 3). Table 1 shows the characteristics in each period, and the median age, disease severity, and duration from onset to admission were significantly different between the three periods. The median age was high in period 3 (1st, 59-year-old; 2nd, 57-year-old; 3rd, 72-year-old), the proportion of moderate/severe cases increased in the latter period (1st, 30.5%; 2nd, 33.3%; 3rd, 41.9%), and the duration from onset to admission was short in period 3 (median: 1st, 8 days; 2nd, 8 days; 3rd, 6 days). Six patients were asymptomatic, with three in period 2 and the others in period 3. The proportion of age was higher in the latter period and 74% of subjects were over 60 years old in period 3 (Fig. 2A). "Healthcare Providers" refers to the individuals who worked in the hospitals, including doctors, nurses, and clerical staff. "Patients/Facilities Users" refers to those who were infected in other hospitals or medical facilities. The rate of Healthcare Providers was higher 43 (27.0%) in period 2 compared to periods 1 and 3 (Fig. 2B). The rate of Patients/Facilities Users was higher in periods 2 and 3 compared to period 1. Lopinavir/ritonavir was often used during the early period. After favipiravir became available, it replaced the use of lopinavir/ritonavir. Since evidence

Table 1 – Characteristics of patients according to study periods.

	Total (n = 260)	Period 1 (n = 46)	Period 2 (n = 159)	Period 3 (n = 55)	p value
Male, n (%)	129 (49.6)	23 (50.0)	77 (48.4)	29 (52.7)	0.858
Age, median (range)	62 (11–99)	59 (22–84)	57 (11–99)	72 (20–92)	0.002
Presence of Pneumonia, n (%)	221 (85.0)	39 (84.8)	137 (86.2)	45 (81.8)	0.839
Severity					
Mild, n (%)	170 (65.4)	32 (69.6)	106 (66.7)	32 (59.2)	0.4208
Moderate, n (%)	55 (21.2)	5 (10.9)	31 (19.5)	19 (34.6)	0.0106
Severe, n (%)	35 (13.5)	9 (19.6)	22 (13.8)	4 (7.3)	0.1922
ECMO[†], n (%)	8 (3.1)	4 (8.7)	3 (1.9)	1 (1.8)	0.0564
Jobs and situations					
Health care provider, n (%)	44 (16.9)	0 (0)	43 (27.0)	1 (1.8)	<0.0001
Inpatients/Medical care facility users, n (%)	54 (20.8)	1 (2.2)	36 (22.6)	17 (30.9)	0.0012
Others, n (%)	162 (62.3)	45 (97.8)	80 (50.3)	37 (67.3)	<0.0001
Nosocomial Infection, n (%)	27 (10.4)	1 (2.2)	21 (13.2)	5 (9.1)	0.2401
Prognosis					
Back at home, n (%)	112 (43.1)	38 (82.6)	48 (30.2)	26 (47.3)	<0.0001
Transferred to an accomodation facilities, n (%)	65 (25.0)	0 (0)	65 (40.9)	0 (0)	0.1402
Transferred to another hospital, n (%)	60 (23.1)	8 (17.4)	34 (21.4)	18 (32.7)	<0.0001
Death, n (%)	15 (5.8)	0 (0)	11 (6.9)	4 (7.3)	0.1799
Still hospitalization	8 (3.1)	0 (0)	1 (0.6)	7 (12.7)	<0.0001
Duration of hospitalization (day), rmedian (range)	13 (1–107)	15 (4–107)	12.5 (1–75)	10 (4–49)	0.1555
Duration from onset to admission (day), median (range)	8 (1–28)	8 (1–27)	8 (1–28)	6 (1–15)	0.0003
Medication (off-label use), n (%)	162 (62.3)	24 (52.2)	99 (62.3)	39 (70.9)	0.1538
Cyclesonidemm, n (%)	128 (49.2)	21 (45.7)	75 (47.2)	32 (58.2)	0.3216
Favipiravir, n (%)	116 (44.6)	11 (23.9)	80 (50.3)	25 (45.5)	0.0065
Ritonavir/Lopiravir, n (%)	11 (4.2)	9 (19.6)	2 (1.3)	0 (0)	<0.0001
Camostat mesilate, n (%)	4 (1.5)	0 (0)	4 (2.5)	0 (0)	0.2752
Nafamostat mesilate, n (%)	9 (3.5)	0 (0)	9 (5.7)	0 (0)	0.0581
Tocilizumab, n (%)	7 (2.7)	0 (0)	0 (0)	7 (12.7)	<0.0001
Remdesivir, n (%)	2 (0.8)	0 (0)	0 (0)	2 (3.6)	0.0234
Predonisolone, n (%)	17 (6.5)	2 (4.4)	7 (4.4)	8 (14.6)	0.0258

ECMO: Extracorporeal membrane oxygenation.

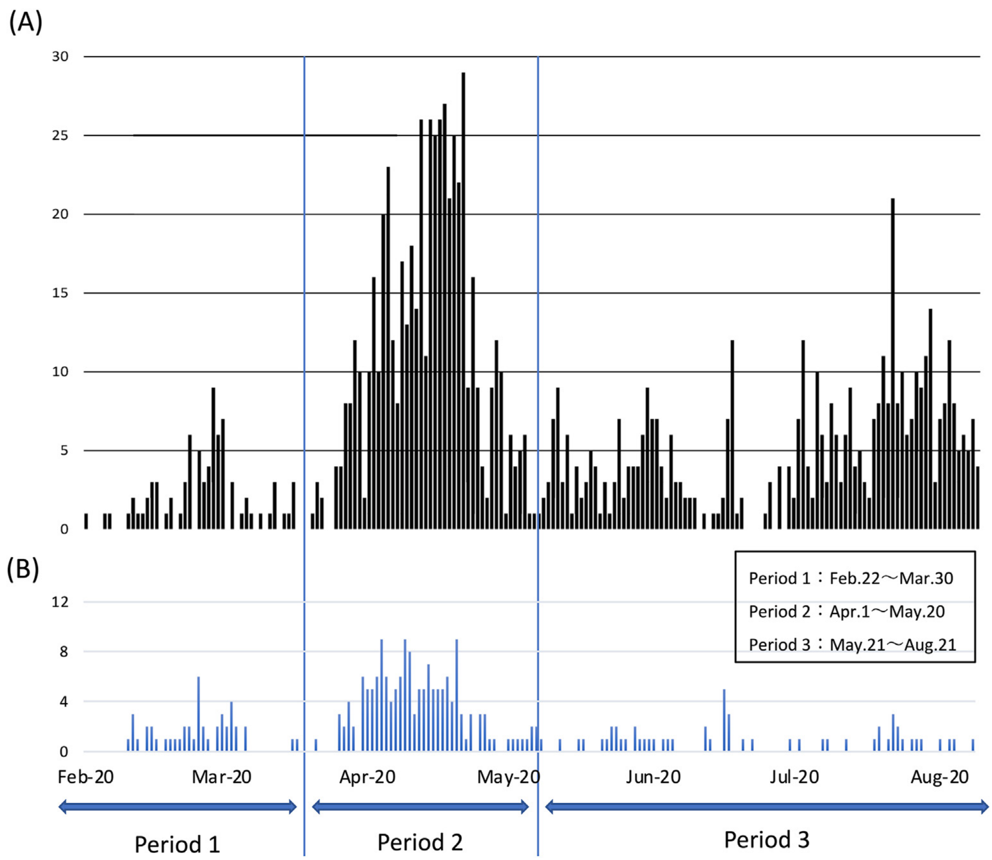

Fig. 1 – (A) The transition of positive PCR tests reported by date in Sapporo city. (B) The transition of the number of the newly admitted patients in two hospitals.

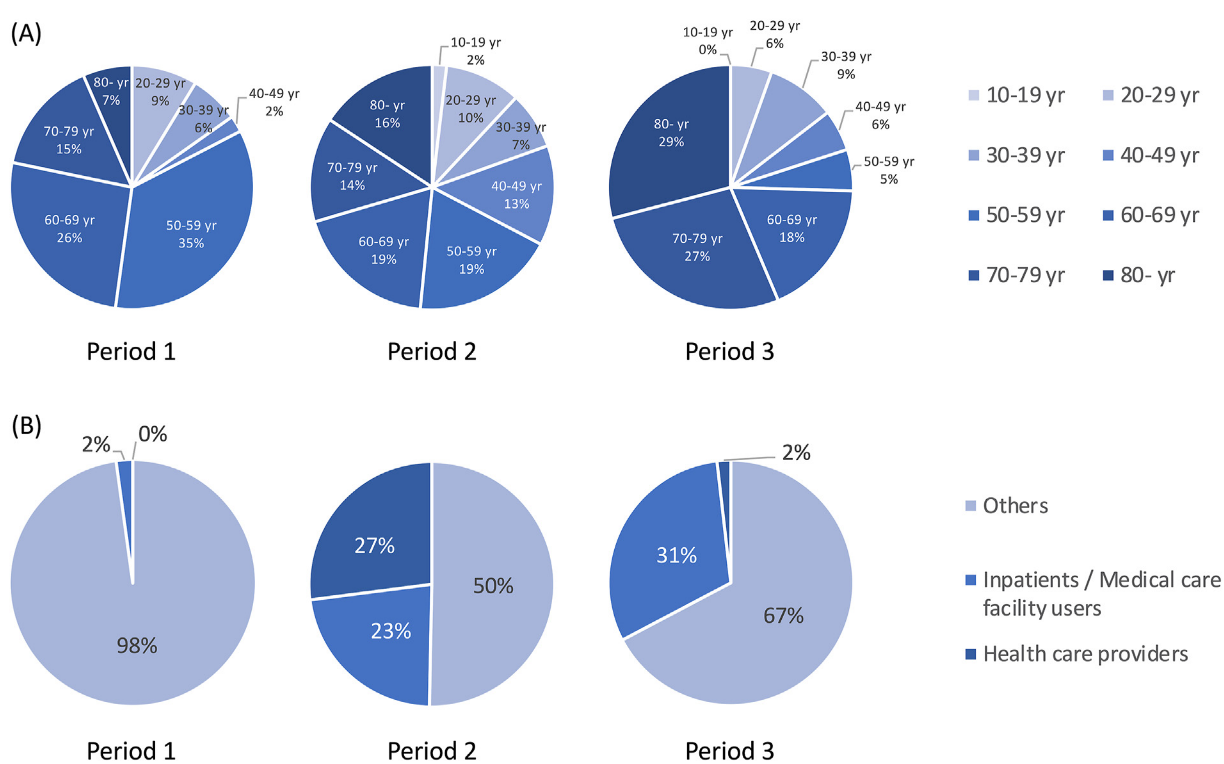

Fig. 2 – (A) Age distribution in each period (B) Proportion of the jobs and situations in each period.

regarding the efficacy of dexamethasone was established, its usage has increased.

3.3. *Comparison of the clinical characteristics of patients according to their jobs and situations*

Table 2 shows the clinical characteristics of the patients by their jobs and situations (Health Providers, Patient/Medical Care Facility Users/Others). Most of the Healthcare Providers had a mild severity (84.1%), younger ages (median 48 years old), and were predominantly female (65.9%). The median age of Patients/Facilities Users was high (79 years old), and more than half of the subjects (64.8%) did not return back to their homes, but were transferred to other hospitals. The duration of the admission period in Patients/Facilities Users was longer (median 23 days) compared to that of the other two groups.

3.4. *Comparison of the clinical characteristics of patients according to the severity of COVID-19*

Table 3 shows the characteristics of subjects according to the disease severity. Patients with a moderate/severe disease were predominantly male. As shown Fig. 3A, those with moderate/severe diseases drastically increased among patients aged >60 years. The number of patients who died of COVID-19 is shown in Fig. 3B; all of them were over 60 years old and consisted of 8–14% of those above 60 years old.

4. Discussion

Changes in social policy due to COVID-19, such as an increase in the number of people who can receive the polymerase chain reaction (PCR) test, changes in discharge criteria, and securing accommodations for patients with mild symptoms, highly influence the characteristics of patients who are admitted to designated hospitals. We thus understand that the analysis in this study does not extrapolate the total characteristics of patients with COVID-19. However, we thought that our evaluation using a survey from the viewpoint of the hospital could provide a new insight, which was not obtained from the information released by the local government. We believe that such an understanding would be helpful if the COVID-19 pandemic spreads in the future or another infectious epidemic arises.

In this study, we obtained three important results from the survey involving patients with COVID-19 who were admitted in two hospitals: 1) we have experienced two waves of COVID-19 to date, probably due to the effect of the declaration of a state of emergency; 2) when we compared the clinical characteristics of patients between the three periods, the rate of Patients/Facilities Users was higher in period 2 and 3 compared to period 1. In addition, the number of Healthcare Providers was higher in period 2 compared to period 1 and 3, and they were younger and predominantly female; 3) Older age was significantly associated disease severity, longer

Table 2 – Characteristics of patients stratified by jobs and situations.

	Health Providers (n = 44)	Inpatients/Medical Care Facility Users (n = 54)	Others (n = 162)	p value
Male, n (%)	15 (34.1)	23 (42.6)	91 (56.2)	0.009
Age, median (range)	48 (21–85)	79 (34–99)	60.5 (11–92)	<0.0001
Presence of Pneumonia, n (%)	35 (79.6)	42 (77.8)	144 (88.9)	0.170
Severity				
Mild, n (%)	37 (84.1)	35 (64.8)	98 (60.5)	0.014
Moderate, n (%)	5 (11.4)	16 (29.6)	34 (21.0)	0.088
Severe, n (%)	2 (4.6)	3 (5.6)	30 (18.5)	0.009
ECMO, n (%)	0 (0)	1 (2.0)	7 (4.3)	0.302
Nosocomial Infection, n (%)	1 (2.3)	26 (48.2)	0 (0)	<0.0001
Prognosis				
Back in home, n (%)	13 (29.6)	13 (24.1)	86 (53.1)	0.0003
Transferred accomodation facilities, n (%)	29 (65.9)	3 (5.6)	33 (20.4)	<0.0001
Transferred anoher hospital, n (%)	2 (4.6)	33 (61.1)	25 (15.4)	<0.0001
Death, n (%)	0 (0)	2 (3.7)	13 (8.0)	0.099
Still hospitalization	0 (0)	3 (5.6)	5 (3.1)	0.125
Duration of hospitalization (day), rmedian (range)	8.5 (2–28)	23 (5–63)	11 (1–107)	<0.0001
Duration from onset to admission (day), median (range)	6 (1–14)	7.5 (1–27)	8 (1–28)	0.095
Medication (off-label use), n (%)	29 (65.9)	27 (50.0)	106 (65.4)	0.111
Cyclesonidemm, n (%)	21 (47.7)	20 (37.0)	87 (53.7)	0.103
Favipiravir, n (%)	23 (52.3)	19 (35.2)	74 (45.7)	0.216
Ritonavir/Lopiravir, n (%)	1 (2.3)	0 (0)	10 (6.2)	0.116
Camostat mesilate, n (%)	2 (4.6)	1 (1.9)	1 (0.6)	0.168
Nafamostat mesilate, n (%)	0 (0)	1 (1.9)	8 (4.9)	0.217
Tocilizumab, n (%)	0 (0)	0 (0)	7 (4.3)	0.114
Remdesivir, n (%)	0 (0)	0 (0)	2 (1.2)	0.544
Predonisolone, n (%)	1 (2.3)	4 (7.4)	12 (7.4)	0.455

ECMO: Extracorporeal membrane oxygenation.

Table 3 – Characteristics of patients according to disease severity.

	Mild (n = 170)	Moderate (n = 55)	Severe (n = 35)	p value
Male, n (%)	74 (43.5)	32 (58.2)	23 (65.7)	0.021
Age, median (range)	54.5 (11–99)	73 (30–96)	63 (22–84)	<0.0001
Presence of Pneumonia, n (%)	135 (79.4)	51 (92.7)	35 (100)	0.011
ECMO, n (%)	0 (0)	0 (0)	8 (22.9)	<0.0001
Jobs and situations				
Health care provider, n (%)	37 (21.8)	5 (9.1)	2 (5.7)	0.015
Inpatients/Medical care facility users, n (%)	35 (20.6)	16 (29.1)	3 (8.6)	0.645
Others, n (%)	98 (57.7)	34 (61.8)	30 (85.7)	0.008
Nosocomial Infection, n (%)	19 (11.2)	7 (12.7)	1 (2.9)	0.173
Prognosis				
Back in home, n (%)	78 (45.9)	28 (50.9)	6 (17.1)	0.003
Transferred accomodation facilities, n (%)	63 (37.1)	2 (3.6)	0 (0)	<0.0001
Transferred anoher hospital, n (%)	27 (15.9)	15 (27.3)	18 (51.4)	<0.0001
Death, n (%)	0 (0)	7 (12.7)	8 (22.9)	<0.0001
Still hospitalization	2 (1.2)	3 (5.5)	3 (8.6)	0.088
Duration of hospitalization (day), rmedian (range)	10 (1–62)	17.5 (4–63)	19 (2–107)	<0.0001
Duration from onset to admission (day), median (range)	8 (1–28)	7 (1–27)	9 (1–21)	0.248
Medication (off-label use), n (%)	82 (48.2)	46 (83.6)	34 (97.1)	<0.0001
Cyclesonidemm, n (%)	61 (35.9)	36 (65.5)	31 (88.6)	<0.0001
Favipiravir, n (%)	46 (27.1)	39 (70.9)	31 (88.6)	<0.0001
Ritonavir/Lopiravir, n (%)	4 (2.4)	2 (3.6)	5 (14.3)	0.006
Camostat mesilate, n (%)	1 (0.6)	2 (3.6)	1 (2.9)	0.222
Nafamostat mesilate, n (%)	0 (0)	0 (0)	9 (3.5)	<0.0001
Tocilizumab, n (%)	1 (0.6)	4 (7.3)	2 (5.7)	0.014
Remdesivir, n (%)	0 (0)	0 (0)	2 (5,7)	0.002
Predonisolone, n (%)	0 (0)	12 (21.8)	5 (14.3)	<0.0001

ECMO: Extracorporeal membrane oxygenation.

duration of admission, and all of the patients who died were over 60 years old.

To our knowledge, there is currently nowhere in the world where the COVID-19 pandemic has occurred in two waves. An outbreak of COVID-19 started in Sapporo city ahead of other areas in Japan, likely due to a large event that took place at the beginning of February. The declaration of a state of emergency following the first outbreak may have prevented another outbreak wave as shown clearly in Fig. 1A and B. Although the exact effect of this declaration is unclear, considering the subsequent lock-down (as in other countries) [5,6], our measures may have inhibited further outbreaks to some extent.

Of note, the clinical features of patients in these three study periods were different. The median age was highest in period 3, and the moderate/severe cases increased in the latter period, probably due to the satisfactory accommodation facilities in Sapporo. The duration from disease onset to admission was short in period 3, probably due to the increase

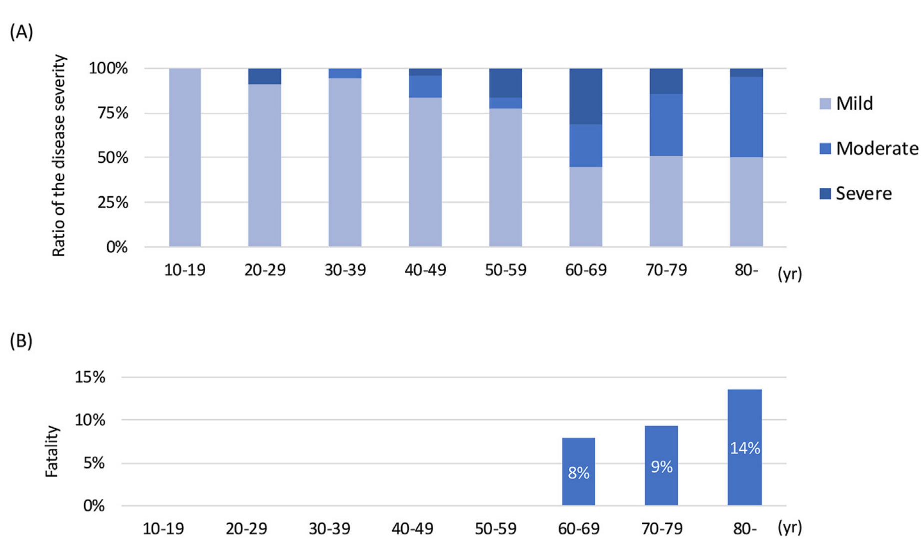

Fig. 3 – (A) Proportion of the disease severity by age. (B) Fatality (percentage of deaths per subjects) by age.

in PCR testing for the extensive survey of subjects with a high-risk contact. Since the second wave occurred mainly in medical facilities, many elderly individuals were included in this period, resulting in a high number of deads. While many Healthcare Providers were also infected in period 2, there have fortunately been no fatalities. However, Suarez-Garcia had reported that healthcare workers who were infected with COVID-19 had less comorbidities, and most of them had a mild clinical course, requiring long periods of sick leaves [7]. We should pay attention to the increase in workload and the additional stress on the already overworked staff who remain in the hospital.

As Japan has conducted fewer polymerase chain reaction (PCR) tests than other major countries, it is difficult to perform a precise comparison of confirmed cases with that of foreign countries. However, considering the fact that the number of deaths per population was high in the U.S. (54 deaths per 100,000 population) and U.K., the number of death in Sapporo City was 55 (2.8 deaths per 100,000 population), which seems to be lower than those in Western countries (https://coronavirus.jhu.edu/data/mortality). Although the exact reasons are still unclear, a number of potential explanations have been discussed. Genetic differences could be the main reason for this big difference [8]. Different lifestyle habit, such as wearing masks and keeping a physical distance, may be involved [9,10]. We recently demonstrated that the results of PCR from saliva is equivalent with that of nasopharyngeal swab samples [11], which may support this explanation. Presence of antibodies prior to January 2020 due to a prior infection by the virus has also been speculated. This study has several limitations. First, this study included only subjects who were diagnosed in two hospitals. In fact, from the second wave onward, over 10 hospitals were designated to treat the patients. Thus, our study may not be representative of the real characteristics of patients with COVID-19 admitted to the hospitals in Sapporo city. Second, not all potential confounding factors that may affect the severity and/or mortality of COVID-19, such as smoking status or co-morbidities, were obtained for all patients. Third, the declaration of a state of emergency that started beginning of April across Japan prohibited movements across prefectures. Thus, the results observed in Sapporo city are not representative of the characteristics of patients in other areas in Japan, particularly in some small islands where industrialization depends on tourism and big medical institutions are not present. Therefore, a customized COVID-19 approach should be provided according to the regions through continuous investigations based on the characteristics of each area. Lastly, although the control of this disease still depends on non-pharmaceutical interventions, a potential treatment has been found: e.g. dexamethasone [4]. These treatment strategies affected the disease severity and outcome even in this short period.

In summary, we clarified the clinical differences of patients with COVID-19 in two hospitals in Sapporo city based on the study period, severity, and patients' job/situation. This survey from the viewpoint of the hospital provides a new insight into and a better guide for the further management of the COVID-19 pandemic.

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Conflict of Interest

The authors report no conflicts of interest for this study.

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